Prosjektoppgave
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TOLERANSE AV IRINOTECAN-BASERT KJEMOTERAPI VED METASTASERENDE KOLOREKTALCANCER. EN RETROSPEKTIV UNDERSØKELSE AV PASIENTER BEHANDLET I EN ONKOLOGISK AVDELING.

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Introduksjon

Epidemiologi og prognose. Kreft i colon og rectum er en av de hyppigst forekommende kreftformene, og i 2003 ble det påvist 2296 nye tilfeller av kolonkreft og 1070 nye tilfeller av rektalkreft i Norge (Kreftregisteret). Halvparten av pasientene får stilt diagnosen tidlig nok til at tilstanden helbredes(1). 5 års overlevelse er om lag 50% (M 49%, K 54%). Bedringen i overlevelse over tid har vært betydelig, fra noe over 30% på slutten av 1950-tallet (2).

Patogenese. Man antar at de fleste tilfeller av kolorektalcancer oppstår fra adenomer. Man snakker om adenom-karsinom sekvens teori som går ut på at det skjer en initiering av tarmepitelet med polyppdannelse, etterfulgt av en vekstfase med økende grad av dysplasi, og til slutt en malign transformasjon. Dette er en utvikling som gjerne kan ta 5-15 år eller mer. Tendensen til malignitet øker med polyppens størrelse, multiple polypper, økende alder og polypper i høyre colonhalvdel. Det er funnet en rekke genetiske endringer (mutasjoner) i sporadiske kolorektale svulster, og de første neoplastiske lesjoner som kan påvises i tarm, er dysplastiske aberrante krypt foci (ACF). Mutasjoner i APC-genet (adenomatosis polyposis-genet) er påvist i disse lesjonene, og antas å være en av de tidligste somatiske genforandringer som kan initiere neoplastisk vekst. Videre er aktivering av K-RAS og/eller inaktivering av APC-genet karakteristiske forandringer i adenomene. Akkumulering av et visst antall genskader i en bestemt rekkefølge er nødvendig for neoplastisk vekst. Andre mutasjoner som er verdt å nevne er tap av kromosom 18, delesjoner av kromosomarm 17p som gir tap av tumor suppressorgenet TP53 og mutasjoner i ”mismatch” reparasjonsystemet.

Behandling. Alle pasienter med diagnostisert kolorektalcancer vil i utgangspunktet gjennomgå radikal eller palliativ kirurgi, med mindre den medisinske tilstanden tilsier at pasienten ikke tåler det eller sykdommen er så framskreden at palliativ kirurgi ikke er tilrådelig. I tillegg til kirurgi som primærbehandling, får pasientene ofte adjuvant behandling som retter seg mot mikroskopisk, ikke klinisk påvisbar sykdom. For coloncancer dreier det seg om adjuvant kjemoterapi, mens for rektumcancer er det stråleterapi kombinert med kjemoterapi som anbefales (2).
For pasienter med metastaserende kolorektalcancer er aktuelle behandlingsformer kirurgi, stråleterapi og kjemoterapi. I tillegg er andre palliative tiltak viktige hos de fleste av disse pasienter. Det dreier seg om behandling av smerter, kvalme, dyspné, dårlig matlyst og dårlig allmenntilstand, samt bedring av tarmpassasje, urinveis- og galleobstruksjon, og tapping/drenasje av ascites, pleuravæske og ev. perikardvæske.Ved påviste fjernmetastaser samtidig med påvisning av primærtumor må man prioritere behandling av den tilstand som truer pasienten mest. Ved coloncancer eller rectumcancer kombinert med operable lever- eller lungemetastaser er det vanligvis riktigst å operere primærtumor (evt. etter preoperativ stråle/kjemoterapi ved rectumcancer) først og senere gjennomføre lever/lungereseksjon. Ved ikke-resektable fjernmetastaser vurderes i hvert enkelt tilfelle nødvendigheten av å operere primærtumor, ut fra symptomer/truende symptomer og forventet levetid (2).

Strålebehandling viser seg å gi lindring av symptomer (som smerter) hos ca. 80 % av pasientene, og vil også kunne utsette plagsomme symptomer dersom den gis når symptomene er i sin begynnelse. Kjemoterapi ved ikke-operabel sykdom er som oftest palliativ, men hos en del pasienter kan effekten være så god at kurativ kirurgi senere kan bli aktuell. De palliative gevinster man kan ha av kjemoterapi i en slik situasjon, er: Symptomlindring og bedret livskvalitet, forlenget symptomfri periode, forlenget levetid og induksjon av objektiv remisjon.
Kjemoterapi ved kolorektalcancer har tradisjonelt sett i Norden vært 5-fluorouracil (5-FU) modulert med kalsiumfolinat. Nye medikamenter som oxaliplatin og irinotecan har nå funnet en plass i førstelinjes behandling av pasienter med metastaser fra colorectal cancer. Hittil er det begrenset dokumentasjon av disse medikamentene i adjuvant sammenheng (2).

Irinotecan. Irinotecan (CPT-11) er en semisyntetisk analog av camptothecin, som opprinnelig kommer fra et kinesisk/tibetansk tre som heter Camptotheca acuminata. Dens cytotoksisitet forårsaker S-fase spesifikt celledrap ved å hemme topoisomerase I i cellen. Dette fører til at DNA-replikasjonen blokkeres og celledeling forhindres. Den ble først oppdaget i Japan i 1983, og den har vist en svært potent antitumor-aktivitet ved en rekke ulike krefttyper, for eksempel kolorektalcancer, øsofaguscancer, ventrikkelcancer, ikke-småcellet og småcellet lungecancer, leukemi og lymfomer, samt gliomer i sentralnervesystemet (3). De viktigste toksiske bivirkninger knyttet til irinotecan er benmargssuppresjon og diaré. Det kan være akutt diaré på grunn av cholinergt syndrom som kommer av hemming av acetylcholinesterase, eller sendiaré som trolig er relatert til akkumulering av den aktive metabolitten av Irinotecan. Av og til kan disse bivirkningene være livstruende, og krever innleggelse, behandling og justering av dosen (3). Irinotecan brukt alene er etablert som 2.linje behandling, etter svikt på 5-FU-basert behandling (2,5,7). Kombinasjonen av irinotecan med 5-FU og kalsiumfolinat er etblert som 1. linjebehandling (2,6).
Irinotecan har en sidekjede i C-10 posisjonen, som kan spaltes av enzymatisk av en karboksylesterase til 7-etyl-10-hydroxycamptothecin (SN-38), som er tusen ganger mer potent enn irinotecan. Irinotecan og SN-38 er i likevekt, en pH- og proteinavhengig likevekt. Karboksylesteraseaktivitet finnes blant annet i serum, lever og tarm. Man antar at det er genetisk variabilitet av karboksylesterase ekspresjon og/eller aktivitet, da SN-38 nivåer varierer fra individ til individ. SN-38 inaktiveres i lever og skilles ut med gallen(3).

Formålet med denne studien var å undersøke omfanget av Irinotecan-relaterte bivirkninger hos pasienter behandlet i en sykehusavdeling. Dessuten ønsket vi å undersøke om graden av Irinotecan-asossierte bivirkninger var avhengig av hvordan Irinotecan ble gitt, alene eller i kombinasjon med 5-FU og kalsiumfolinat. Således har vi undersøkt bivirkningene ved FLIRI- og FOLFIRI-regimene og Irinotecan gitt alene, og undersøkt om det er forskjeller i bivirkninger mellom de tre regimene. Vi har registrert bivirkninger av hematologisk og ikke-hematologisk karakter og har lagt størst vekt på toksisitetstegn som diaré-plager og nøytropeni.

Pasienter og metoder

Pasientutvelgelse

Denne studien er gjort retrospektivt, dermed er all pasientinformasjon hentet ut fra journaler. Pasienter under FLIRI- og FOLFIRI- regimet inngår i en fase III-studie, og dette gjør disse pasientgruppene like når det gjelder utvelgelse. Felles for alle pasientene, også de som har fått Irinotecan alene, er histologisk bekreftet diagnose adenocarsinom i colon eller rectum, samt metastaser uegnet for radikaloperasjon. Andre inklusjonskriterier for alle tre regimene var: alder 18-75 år, WHO-grad 0-2 ved oppstart, forventet levetid mer enn 3 måneder, adekvate hematologiske verdier (hemoglobin ≥ 10 g/dl, nøytrofile ≥ 2 x 10^9/l og trombocytter ≥ 150 x 10^9/l) tilfredstillende nyre- og leverfunksjon (kreatinin < 1.25 x øvre normalgrense, ASAT og ALAT < 3 x øvre normalgrense [< 5 x øvre normalgrense ved levermetastaser], total-bilirubin < 1.25 x øvre normalgrense [< 1.5 x øvre normalgrense ved levermetastaser]) (4).
Når det gjaldt pasientene under FLIRI- og FOLFIRI-regimet hadde ingen hatt tidligere kjemoterapi eller kun adjuvant kjemoterapi som ble fullført minimum 6 måneder før oppstart av aktuelle kjemoterapi og ingen strålebehandling siste 4 uker før oppstart av kjemoterapi (4).
Før oppstart av behandling, gjenomgikk pasientene evaluering med full anamnese, somatisk undersøkelse, blodprøveundersøkelse, komplett tumorvisualisering (røngten, CT og ultralyd) og tumormarkører.
Irinotecan gitt alene har i motsetning til FLIRI og FOLFIRI, blitt gitt som 2.linjebehandling utenom studie. Vår utvelgelse av pasienter i denne gruppen skjedde ut fra oversikt over behandlede pasienter i onkologisk avdeling ved Ullevål universitetssykehus.

Behandlingen

I de tre pasientgruppene er Irinotecan gitt på ulike måter, som del av kombinasjonsbehandling ved FLIRI- og FOLFIRI-regimet, og i siste regime er Irinotecan gitt som eneste medikament.
Ved FLIRI-regimet ble pasienten på dag 1 behandlet med Irinotecan 180 mg/m2 administrert i.v. over 60 min, umiddelbart etterfulgt av 5-FU 500 mg/m2 som i.v. bolus, 30-40 min senere av Leukovorin 60 mg/m2 som i.v. bolus over 5-10 min. 5-FU/Leukovorin-dosene ble gjentatt dag 2.
Pasientene i FOLFIRI-gruppen ble dag 1 gitt Irinotecan 180 mg/m2 i.v. i løpet av 1 time. Dette ble etterfulgt av Kalsiumfolinat 200 mg/m2 administrert i.v. over et tidsrom på 2 timer. Deretter ble 5-FU 400 mg/m2 gitt som i.v. bolus og så 600 mg/m2 administrert i.v. i baxterpumpe over 22 timer. Kalsiumfolinat- og 5-FU-dosene ble gjentatt dag 2.
Ved siste regimet ble pasientene kun behandlet med Irinotecan. Dette ble administrert som 350 mg/m2 i.v. over 1 time kun 1 dag.
For FLIRI- og FOLFIRI-regimet ble behandlingen gjentatt hver 14.dag, mens Irinotecan-kurene ble gitt hver 3.uke, inntil sykdomsprogresjon eller uakseptable toksisitetstegn oppstod.
Dosejustering av Irinotecan/utsettelse av kur ble utført i tilfeller med alvorlige hematologiske og/eller ikke-hematologiske bivirkninger.

Som profylakse ble pasientene i alle tre regimene premedisinert med Zofran 8 mg x 2 mot kvalme, samt Atropin 0,25 mg s.c. før oppstart med Irinotecan for å forhindre akutt cholinergt syndrom. Ved tegn til utvikling av cholinergt syndrom til tross for profylaktisk behandling, ble Atropin-dosen gitt på ny. Resept på Imodium ble gitt for behandling av eventuell diare oppstått i tiden mellom kurene.
Pasienter med alvorlig diare, eventuelt i kombinasjon med kvalme, feber eller nøytropeni, ble innlagt for antibiotika-behandling og rehydrering. Febril nøytropeni krevde også sykehusinnleggelse for behandling med antibiotika.

Evaluering av toksisitet

For gradering av toksisitet ble National Cancer Institute common toxicity criteria (NCI-CTC, versjon 2.0) brukt som utgangspunkt. Før hver kur ble det tatt blødprøver for hematologi, samt anamnestisk kartlegging av bivirkninger som diare, kvalme og oppkast, tegn til infeksjon og feber og andre mulige bivirkninger som vekttap og håravfall. I tillegg ble pasienten under behandlingsforløpet spurt om å vurdere sin egen allmenntilstand og fungering i dagliglivet, gradert som WHO-status. Dette er informasjonen som er lagt til grunn for vår evaluering av toksisitet. Vi har valgt å legge vekt på hematologiske verdier og feber og infeksjoner, subjektive plager i form av diare, kvalme og oppkast og cholinergt syndrom, samt WHO-status.

Statistisk analyse

For å vurdere om forskjellene i toksisitet mellom de tre regimene er statistisk signifikante har vi brukt kji-kvadrattest. Sammenligningene har vært mellom Irinotecan gitt alene på den ene siden og kombinasjonsbehandling, FLIRI- og FOLFIRI-regimene, på den andre siden. Vi har tatt for oss toksisitetstegn som nøytropeni og diaré, samt sett på om det er statistisk signifikante forskjeller i antallet utsatte kurer på grunn av subjektivt besvær. P-verdier lavere enn 0,05 regnes som signifikante.

Resultater

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Pasientkarakteristikk

Totalt 30 pasienters behandlingsforløp ble lagt til grunn for denne undersøkelsen. Disse pasientene er fordelt likt på de tre regimene, det vil si 10 pasienter på hvert av regimene (tabell 1). Pasientene er registrert med hensyn til alder og kjønn. Det er tatt i betraktning hvilken WHO-status pasientene hadde før oppstart av behandlingen og antall organer hos hver enkelt pasient med påvisbare metastaser, som mål på grad av sykdom ved behandlingsstart. Da Irinotecan alene er 2.linjebehandling, har disse pasientene mottatt kjemoterapi for metastaserende sykdom tidligere, mens tre pasienter i FLIRI-regimet og to pasienter i FOLFIRI-regimet har fått adjuvant kjemoterapi før aktuelle behandling.

Tabell 1 Pasientkarakteristika

	FLIRI	***FOLFIRI***	***IRINOTECAN***
Antall pasienter	10	10	10
Alder*	61(44-71)	62(52-71)	57 (45-66)
Kjønn			
Mann	7	6	6
Kvinne	3	4	4
WHO-status**			
Grad 0	4	8	5
Grad 1	6	2	5
Metastasering til ant organer			
1	3	5	4
2	5	5	6
3	2	0	0

*Alderen er oppgitt som gjennomsnittsalder og spredning av alder.
**I noen journaler manglet dokumentasjon og vurdering av WHO-status, og i disse tilfellene har vi valgt å tolke for eksempel beskrivelser som ”god allmenntilstand” som grad 0, og ”rimelig god allmenntilstand” som grad 1.

Kurer og doser

Tabell 2 viser at spredningen på antall kurer gitt per pasient er relativt stor. Effekten av kjemoterapien, både den subjektive og objektive, blir vurdert hver 6.-8. uke. Årsakene til seponering er forskjellige, enten subjektivt besvær i form av diaré eller fatigue, eller manglende røntgenologiske tegn på effekt.

Tabell 2 Oversikt over kurer og doser

	FLIRI	*FOLFIRI*	*IRINOTECAN*
Ant kurer totalt	125	131	87
Ant kurer per pasient	12,5 (4-23)	13,1 (3-28)	8,7 (2-17)
Dose gitt/planlagt dose	87,7% (70%-100%)	91,3% (80%-100%)	98,2% (88%-100%)

Alle pasientene skal i utgangspunktet ha en dose beregnet ut i fra kroppsoverflate (satt til 100%). Hvis paienten får mye bivirkninger i form av for eksempel diaré, kvalme, oppkast, tretthet eller benmargshemming, reduseres dosen. Vi har regnet ut den gjennomsnittlige dosen for hver pasient, altså hvor mange prosent de har fått i forhold til opprinnelig beregnet dose. Deretter regnet vi gjennomsnittet av alle pasientenes doser i hvert regime, og det er disse tallene som står i tabellen. Vi fant at FLIRI og FOLFIRI har lavest gjennomsnittlig dose i forhold til planlagt dose, noe som tyder på flere dosereduksjoner.

Årsaker til seponering

Tabell 3 er en oversikt over årsakene til seponering av kjemoterapien. Under subjektive plager finner vi stort sett diaré-problemer og dårlig allmenntilstand. Progresjonen bedømmes røntgenologisk. Det gjøres billeddiagnostikk vanligvis åtte uker etter behandlingsstart i FLIRI og FOLFIRI, og etter seks uker med Irinotecan alene. Progresjonen vurderes ut i fra WHO-kriterier, og en økning i summen av produktene av to diametere av de målbare lesjoner på 25% eller mer sammenlignet med tidligere bilder, fører til seponering. Alle unntatt en pasient som fikk Irinotecan alene seponerte behandlingen på grunn av manglende respons. Antallet som fikk behandlingen seponert på grunn av subjektive plager, var henholdsvis fire og tre i FLIRI- og FOLFIRI-regimet. Det er ikke umulig at disse pasientene også hadde progresjon, men det var ikke den umiddelbare årsaken til seponering.

Tabell 3 Årsaker til seponering av behandlingen

	FLIRI	*FOLFIRI*	*IRINOTECAN*
Subjektive plager	4	3	1
Progresjon	3	3	9
Planlagt avsluttet/tilfredsstillende resultat	3	3	-
Andre	-	1*	-

*avbrutt pga hjerteinfarkt. Vi vet ikke hvorvidt dette kan være en toksisk effekt.

Tre pasienter i både FLIRI- og FOLFIRI-regimet hadde tumorprogresjon som var direkte årsak til seponering. Vi fant at tre pasienter i hvert av regimene FLIRI og FOLFIRI fikk behandlingen seponert fordi behandlingsresultatene var tilfredsstillende nok til å ta en pause i behandlingen eller fordi de skulle opereres. En pasient avsluttet sin FOLFIRI-behandling fordi han fikk hjerteinfarkt. Dette kan være forårsaket av toksisitet.

Hematologisk toksisitet

Nøytropeni er det hematologiske toksisitetsparameteret som tillegges størst oppmerksomhet, da dette er svært sentralt og dosebegrensende. Alvorlig nøytropeni kan føre til infeksjoner og innleggelser, og dette gjør nøytropeni til et av de viktigste målene for dosereduksjon og utsettelse av kur. Grad 1-2 nøytropeni tilsvarer verdiene 1.0-1.9, og er relativt utbredt. Dette er målt hos seks pasienter etter 22 % av kurene i FLIRI-regimet, hos 5 pasienter etter 22 % av kurene i FOLFIRI-regimet, mens det er målt hos 2 pasienter etter 10.3 % av Irinotecan-kurene (tabell 4).

Tabell 4 Hematologisk toksisitet

	FLIRI			***FOLFIRI***			***IRINOTECAN***		
	Antall pasienter	**Antall kurer**	**%**	**Antall pasienter**	**Antall kurer**	**%**	**Antall pasienter**	**Antall kurer**	**%**
Nøytropeni									
Grad 1-2	6	28	22	5	29	22	2	9	10.3
Grad 3	2	2	1.6	-	-	-	1	1	1.2
Grad 4	-	-	-	-	-	-	-	-	-
Febril nøytropeni*	2	2	1.6	1	1	0.8	-	-	-
Infeksjon med nøytropeni grad 3-4	1	1	0.8	-	-	-	1	1	1.2
Utsatte kurer pga nøytopeni	5	12	9.6	4	5	3.8	1	2	2.3
Leukopeni									
Grad 1-2	5	22	18	1	18	14	2	10	11.5
Grad 3	3	3	2.4	1	1	0.8	-	-	-
Grad 4	-	-	-	-	-	-	-	-	-
Trombocytopeni grad 1-2	2	6	4.8	3	22	17	2	12	13.8
Anemi									
Grad 1	8	58	46	7	36	27	5	20	23
Grad 2	3	3	2.4	3	17	13	1	1	1.2

*Definert som feber lik eller høyere enn 38 grader med grad 3-4 nøytropeni i mangel på dokumentert infeksjon.

Grad 3 nøytropeni tilsvarer nøytrofile 0.5-0.9, og har vært observert hos 2 pasienter i FLIRI-regimet (1.6% av kurene), hos ingen i FOLFIRI-regimet og hos 1 pasient i Irinotecan-regimet (1.2% av kurene), uten at pasientene har hatt tegn til feber eller infeksjon.
Febril nøytropeni er definert som feber lik eller høyere enn 38 grader med grad 3-4 nøytropeni i mangel på dokumentert infeksjon, og er observert hos 2 pasienter i FLIRI-regimet (1.6% av kurene) og hos 1 pasient i FOLFIRI-regimet (0.8% av kurene), mens det ikke er observert i Irinotecan-regimet. Infeksjon med nøytropeni grad 3-4 har imidlertid rammet 1 pasient i både FLIRI- og Irinotecan-regimet etter henholdsvis 0.8% og 1.2% av kurene.
Utsettelse av kur skal i følge retningslinjene utføres ved nøytrofile < 1.5, det vil si ved grad 2-4 nøytropeni. Vi har allikevel ved enkelte tilfeller sett at pasienter med nøytropeni grad 2 har fått kur til planlagt tid. Ved FLIRI-regimet har 5 pasienter fått utsatt 9.6% av totalt antall kurer, ved FOLFIRI-regimet har 4 pasienter fått utsatt 3.8% av totalt antall kurer og ved Irinotecan-regimet har 1 pasient fått utsatt 2.3% av totalt antall kurer grunnet nøytropeni.
Det er statistisk signifikant forskjell ved sammenligning av Irinotecan gitt alene og de to kombinasjonsregimene når det gjelder totalt antall kurer som har gitt nøytropeni uansett grad (FLIRI: p=0.02, FOLFIRI: p=0.04). Det er også statistisk signifikant forskjell mellom FLIRI-regimet og Irinotecan gitt alene med hensyn til antall utsatte kurer grunnet nøytropeni (p=0.04).

Det er også etter hver kur registrert totalt antall leukocytter. Disse verdiene følger til en stor grad verdiene for nøytrofile, og er lagt mindre vekt på i vår vurdering. Verdiene er listet opp i tabell 4.

Trombocytter er vurdert etter gitt kur, og vi har ikke funnet verdier som tilsvarer alvorlig trombocytopeni i noen av regimene. Trombocytopeni grad 1-2 har ikke fått konsekvenser i form av dosereduksjon eller utsettelse av kur.

Lettgradig anemi er en utbredt bivirkning. Grad 1 anemi tilsvarer Hb 10-11.5 g/dl hos kvinner og 10-12.5 g/dl hos menn, og er registrert hos åtte pasienter etter 46% av kurene i FLIRI-regimet, hos syv pasienter etter 27% av kurene i FOLFIRI-regimet og hos fem pasienter etter 23% av kurene i Irinotecan-regimet.
Anemi med Hb 8.0-9.9 g/dl tilsvarer grad 2. Dette er observert hos tre pasienter i FLIRI-regimet (2.4% av kurene), hos tre pasienter i FOLFIRI-regimet (13% av kurene) og hos en pasient i Irinotecan-regimet (1.2% av kurene).

Ikke-hematologisk toksisitet

Diaré er det mest utbredte subjektive toksisitetstegn, og også den bivirkningen som er best beskrevet i journalene. Diaré grad 1 tilsvarer en økning i antall avføringer med 2-3 per dag og forekommer hyppig i alle tre regimene (tabell 5). Hele åtte pasienter i FLIRI- og FOLFIRI-regimet har hatt diaré grad 1, mot seks pasienter som fikk Irinotecan alene. Andel kurer som ga diaré grad 1 var 24% i FLIRI-regimet, 24% av kurene med Irinotecan alene og 32% i FOLFIRI-regimet. Grad 2 er en økning til 4-6 avføringer per dag, nattlig avføring eller moderate magekramper. I FLIRI-regimet var det 4 pasienter (3.2% av kurene) og i FOLFIRI-regimet var det 2 pasienter (1.5% av kurene) med grad 2. Grad 3 klassifiseres som 7-9 avføringer om dagen, evt inkontinens eller alvorlige magekramper. Henholdsvis 1 pasient (0.8% av kurene) og 2 pasienter (1.5% av kurene) fikk grad 3 i FLIRI-regimet og FOLFIRI-regimet. Grad 4 er 10 eller flere episoder i løpet av 24 timer, blodig diaré eller behov for parenteral ernæring. I FLIRI-regimet var det ingen pasienter med grad 4 diaré, sammenlignet med to pasienter i FOLFIRI-regimet. Ingen pasienter som ble gitt Irinotecan alene hadde diaré grad 2 og 3, men en pasient hadde grad 4. Ulikhetene mellom de tre regimene er ikke statistisk signifikante når det gjelder diaré.

Tabell 5 Ikke-hematologisk toksisitet

	FLIRI			***FOLFIRI***			***IRINOTECAN***		
	Antall pasienter	Antall kurer	%	Antall pasienter	Antall kurer	%	Antall pasienter	Antall kurer	%
Diaré									
grad 1	8	30	24	8	42	32	6	21	24
grad 2	4	4	3.2	2	2	1.5	-	-	-
grad 3	1	1	0.8	2	2	1.5	-	-	-
grad 4	-	-	-	2	2	1.5	1*	1	1.1
Kvalme									
grad 1	4	13	10.4	5	31	24	5	14	16
grad 2	4	6	4.8	3	3	2.3	-	1	1.1
grad 3	-	-	-	1	2	1.5	1	1	1.1
Oppkast									
grad 1	1	3	2.4	3	4	3.1	-	-	-
grad 2	2	2	1.6	-	-	-	-	-	-
grad 3	-	-	-	-	-	-	1	1	1.1
Cholinergt syndrom	-	-	-	2	2	1.5	4	4	4.6
Utsatte kurer pga subj bivirkn	2	2	1.6	4	6	4.6	1	1	1.1
Innleggelser	2	3	2.4	5	7	5.3	1	1	1.1

*Innlagt med toksisk gastroenteritt, som vi antar er grad 4 ut fra beskrivelse.

Kvalme er også en hyppig bivirkning ved kjemoterapi. De fleste tilfellene er imidlertid mild kvalme, grad 1 hvor pasienten fortsatt klarer å spise tilnærmet normalt. Uttalt kvalme som gjør at pasienten ikke klarer å få i seg næring på egen hånd klassifiseres som grad 3. Vi fant en pasient i FOLFIRI-regimet (1.5% av kurene) og en pasient som fikk Irinotecan alene (1.1% av kurene) med grad 3 kvalme.

Oppkast graderes i hovedsak etter antall episoder i løpet av 24 timer, grad 1 er én episode, grad 2 er 2-5 episoder, grad 3 er 6-10 episoder, og 10 eller flere episoder eller behov for parenteral ernæring klassifiseres som grad 4. En pasient i FLIRI-regimet (2.4% av kurene) og tre pasienter i FOLFIRI-regimet (3.1% av kurene) ble registrert til å ha grad 1. Grad 2 var det to pasienter i FLIRI-regimet (1.6% av kurene) som hadde, og en pasient med grad 3 som fikk Irinotecan som eneste behandling (1.1% av kurene). Ingen pasienter var registrert med grad 4.

Cholinergt syndrom er en umiddelbar reaksjon til infusjon av Irinotecan. Symptomet er magesmerter og eventuelt akutt diaré. Behandlingen er atropin. Ingen pasienter med FLIRI-regimet fikk cholinergt syndrom, mot to og fire pasienter som fikk henholdsvis FOLFIRI og Irinotecan alene.

Vi har også registrert hvor mange kurer som ble utsatt på grunn av subjektive plager, og vi fant at to pasienter i FLIRI-regimet, fire pasienter i FOLFIRI-regimet og en pasient som fikk Irinotecan alene fikk en eller flere kurer utsatt. Den prosentvise andelen kurer som har blitt utsatt er henholdsvis 1.6%, 4.6% og 1.1% i de tre regimene.

Når det gjelder årsakene til innleggelser i løpet av behandlingen er disse ganske varierte. I FLIRI-regimet er det registrert to pasienter som ble innlagt og tre innleggelser totalt (2.4%). Den ene pasienten ble lagt inn to ganger, en gang med DVT og andre gang på grunn av nedsatt allmenntilstand, mens den andre pasienten ble lagt inn for væske- og antibiotikabehandling. I FOLFIRI-regimet ble fem pasienter innlagt, og antall innleggelser totalt er 7 (5.3%). To innleggelser var grunnet i infeksjon, resten hadde subjektive bivirkninger i form av obstipasjon, diaré, kvalme og magesmerter. Av pasienten som fikk Irinotecan alene ble kun en pasient innlagt en gang, og årsaken var toksisk gastroenteritt.

Diskusjon

Dette er en retrospektiv undersøkelse, hvor benyttede opplysninger er hentet fra pasientjournal. Den har totalt omfattet 30 pasienter som alle har fått Irinotecan-basert kjemoterapi. Pasientene er fordelt på tre behandlingsregimer, 10 pasienter i hvert regime. I FLIRI- og FOLFIRI-regimet er Irinotecan gitt i kombinasjon med kalsiumfolinat på ulike måter og i siste gruppe er Irinotecan gitt som eneste medikament. FLIRI- og FOLFIRI-regimet er etablert 1.linjebehandling ved metastaserende kolorektalcancer, mens Irinotecan alene gis ved svikt på 5-FU-basert behandling, dermed som 2.linjebehandling. Gruppene er derfor ikke fullstendig sammenlignbare da utgangspunktet for behandling er ulik. Pasientene i alle tre gruppene er imidlertid vurdert til å ha WHO-status grad 0-1 og omtrent samme grad av metastasering (tabell 1) som mål for sykdomsstadium.

Formålet med studien var å undersøke hvordan pasientene tolererte behandlingen. Det er lagt vekt på hvilke bivirkninger som er de hyppigste, og i hvilken utstrekning de har oppstått i forhold til antall pasienter og kurer. Som nevnt er studien gjort retrospektivt, og ulike rutiner for og mangelfull journaldokumentasjon, er et usikkerhetsmoment ved studien.

Det var også av interesse å undersøke om det var målbare ulikheter mellom de tre regimene, da spesielt om Irinotecan alene ga et annet toksisitetsnivå enn FLIRI- og FOLFIRI-regimet. Det er en vanlig oppfatning i det kliniske miljøet at Irinotecan gir mer og alvorligere bivirkninger gitt alene, sett i forhold til Irinotecan som del av kombinasjonsbehandling. Da det er få pasienter som inngår i undersøkelsen, er det er usikkert om resultatene er representative for større grupper, og tillegg begrenser det muligheten til å konkludere om påviste forskjeller faktisk er reelle, basert på statistisk analyse.

Resultatene viser at pasientene generelt i alle tre gruppene tolererte Irinotecan-basert kjemoterapi godt. Tabell 2 viser at Irinotecan alene er gitt i gjennomsnittlig færre kurer enn hva som er tilfellet for FLIRI- og FOLFIRI-regimet (8.7 mot henholdsvis 12.5 og 13.1). Siden Irinotecan gis hver 3.uke mot hver 2.uke i de to andre regimene, er total behandlingstid relativt lik.
Dose gitt/planlagt dose-ratio var 87.7 %, 91.3 % og 98.2 % for henholdsvis FLIRI, FOLFIRI og Irinotecan alene. Dette gir en pekepinn om at flere dosereduksjoner var nødvendig i FLIRI- og FOLFIRI-regimet enn for Irinotecan alene. Grunnlaget for dosereduksjonen var nøytropeni grad 2-4 eller sterkt subjektivt besvær.
Bivirkninger var årsak til seponering hos en viss andel av pasientene, denne andelen er forskjellig for de uilke regimene og gjenspeiler også dosereduksjonsandelen som beskrevet over. Av pasientene i FLIRI-gruppen avsluttet fire behandlingen grunnet subjektive plager, det samme gjaldt tre pasienter i FOLFIRI-gruppen, mens kun en pasient som mottok Irinotecan alene, seponerte behandling grunnet subjektivt besvær.
Som forventet, basert på tidligere studier, var nøytropeni og diare de vanligste bivirkningene i alle tre regimene. Grad 1-2 nøytropeni var klart hyppigste grad av nøytropeni, og rammet seks pasienter i FLIRI-regimet (22 % av kurene), fem pasienter i FOLFIRI-regimet (22 % av kurene), mens kun to pasienter som mottok Irinotecan alene (10.3 % av kurene) hadde grad 1-2 nøytropeni.

Glimelius et al. har vist ved en større fase II studie med 74 pasienter inkludert, at 39 % av FLIRI-kurene ga grad 1-2 nøytropeni, mens 15 % og 2 % av kurene ga henholdsvis grad 3 og 4 nøytropeni (4). For FOLFIRI-regimet viser studie av Douillard et al. at 71.2 % av pasientene hadde nøytropeni, 28.8% hadde grad 3-4 (6). Cunningham et al. fant i studie av Irinotecan alene at 22% av pasientene hadde grad 3-4 nøytropeni (7). Vår studie viser at ingen pasienter har hatt grad 4 nøytropeni uten infeksjon eller feber, og at to pasienter i FLIRI-regimet (1.6 % av kurene), og en pasient som har mottatt Irinotecan alene (1.2 % av kurene) hadde grad 3 nøytropeni. Febril nøytropeni oppstod hos to pasienter i FLIRI-regimet (1.6 % av kurene) og hos en pasient i FOLFIRI-regimet (0.8 % av kurene), mens ingen av pasientene som fikk Irinotecan alene ble rammet. Imidlertid hadde en pasient i FLIRI-regimet (0.8 % av kurene) samt en pasient behandlet med Irinotecan alene (1.2% av kurene) et tilfelle hver av infeksjon med samtidig nøytropeni grad 3-4. Andre studier viser at i FLIRI-regimet ga 0.2 % av kurene febril nøytropeni og 1 % av kurene infeksjon med grad 3-4 nøytropeni (4). Når det gjelder FOLFIRI-regimet viser Douillard et al. at 9.3 % av pasientene hadde febril nøytropeni og 3.7 % hadde infeksjon med grad 3-4 nøytropeni (6). 3 % av pasientene som fikk Irinotecan alene i studien av Cunningham et al. hadde feber eller infeksjon og grad 3-4 nøytropeni (7). Selv om insidensen av alvorlig nøytropeni er lav i alle tre regimene i vår studie, og viser lite differanse mellom regimene, er det statistisk signifikant forskjell mellom Irinotecan alene sammenlignet med begge de to andre gruppene når det gjelder totalt antall kurer som har gitt nøytropeni uansett grad (for FLIRI p=0.02, for FOLFIRI p=0.04).
Konsekvensen av nøytropeni er registrert som utsatte kurer grunnet nøytropeni grad 2-4. 9.6 % av kurene i FLIRI- regimet, 3.8 % av kurene i FOLFIRI-regimet og 2.3 % av Irinotecan-kurene ble utsatt grunnet nøytropeni. Dette gir en statistisk signifikant forskjell mellom FLIRI-regimet og Irinotecan alene (p=0.04), men ikke mellom FOLFIRI-regimet og Irinotecan alene.
Andre hematologiske toksisitetstegn som leukopeni, trombocytopeni og anemi har ikke hatt konsekvenser for dosereduksjon eller doseutsettelse i noen av regimene.

Mild diaré grad 1 er svært hyppig i alle tre regimene. 24 % av kurene i FLIRI-regimet (åtte pasienter), 32 % av kurene i FOLFIRI-regimet (åtte pasienter) og 24 % av kurene hvor Irinotecan er gitt alene (seks pasienter) var etterfulgt av grad 1 diare. Alvorligere diaré grad 3-4 er mindre utbredt, og en pasient i FLIRI-regimet hadde grad 3 diaré (0.8 % av kurene), to pasienter i FOLFIRI-regimet hadde grad 3 diaré og to pasienter hadde grad 4 diaré (1.5 % av kurene grad 3 og 1.5 % av kurene grad 4) og en pasient behandlet med Irinotecan alene hadde grad 4 diaré (1.1 % av kurene). Det er ingen statistisk signifikant forskjell på de tre regimene når det gjelder diaré. Glimelius et al. har i sin studie av FLIRI-regimet kun registert grad 3-4 diaré, og 1.7 % av kurene ga dette (4). FOLFIRI-studien av Douillard et al. viser at 88.9 % hadde diaré, 44.4% hadde grad 3 eller 4 (6). 22 % av pasientene som fikk Irinotecan alene i studien av Cunningham et al. hadde diaré grad 3-4 (7).
Kvalme er også en utbredt bivirkning og de fleste registrerte tilfellene er av mild grad. Kun en pasient i FOLFIRI-regimet og en pasient behandlet med Irinotecan alene hadde kvalme grad 3. Oppkast var lite utbredt i alle tre regimene, og det ble registrert kun en pasient med grad 3 oppkast, denne pasienten fikk Irinotecan alene.

Det var ikke et mål i denne studien å legge vekt på objektiv respons av behandlingen, og da det kun er 30 pasienter som inngår i studien, er det ikke tilstrekkelig datagrunnlag for å fastslå responsrate. Tidligere studier med større pasientmateriale er utført med formål å undersøke responsrate. Objektiv respons av FLIRI-regimet registrert i fase II-studie utført av Glimelius et al. viser en total responsrate på 43 % (4). Responsrate for FOLFIRI-regimet var 49 % i studie av Douillard et al. (6). Saltz et al. finner responsrate 29 % for Irinotecan alene (8).

Det har blitt hevdet at Irinotecan alene gir et høyere toksisitetsnivå enn gitt som kombinasjonsbehandling. Ut fra våre resultater ser det ut til at Irinotecan alene er mindre toksisk enn forventet. Irinotecan gitt alene gir statistisk signifikant mindre nøytropeni uansett grad, sammenlignet med FLIRI-regimet ($p=0.02$) og FOLFIRI-regimet ($p=0.04$). Vi finner også statistisk signifikant færre utsatte kurer grunnet nøytropeni for Irinotecan alene i forhold til FLIRI-regimet ($p=0.04$).
Når det gjelder mild grad av diaré, er dette også en hyppig bivirkning i alle tre regimene. Vi finner imidlertid ingen statistisk signifikant forskjell mellom regimene når det gjelder diaré. Sammenlignet med tidligere studier utført på de tre regimene, viser våre resultater gjennomgående lavere bivirkningsfrekvens. Når det gjelder diaré og andre typer subjektive bivirkninger, kan dette muligens forklares av dårlig og lite detaljert rapportering i pasientjournalene. Spesielt kan dette ha hatt betydning for Irinotecan alene, da disse pasientene ikke har inngått i en formell studie, og det dermed ikke er lagt like stor vekt på korrekt journalføring enn for de pasientene som har vært en del av en studie. Dette er imidlertidig ikke like aktuelt når det gjelder nøytropeni, da disse verdiene er godt dokumentert og ikke gjenstand for fortolkning.
En annen årsak til at vi finner mindre bivirkninger, kan være at pasientene som har inngått i vår studie har hatt bedre allmenntilstand, enn hva som er tilfelle ved tidligere utførte studier. Vi registrerte at samtlige pasienter hadde WHO grad 0-1 ved oppstart av behandling, mens også en mindre gruppe pasienter med WHO-grad 2 har inngått i de sammenlignbare studiene. Det må også nevnes at vi ved denne undersøkelsen har hatt betydelig mindre pasientmateriale enn ved tidligere utførte studier på hvert av de tre regimene. Dette gjør at vi må vurdere våre konklusjoner med varsomhet.

Sett under ett, viser vår studie at pasientene generelt tolererer Irinotecan-basert kjemoterapi godt. Vi finner relativt små forskjeller mellom de tre regimene både når det gjelder hematologiske og ikke-hematolgiske bivirkninger.

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Vedlegg

1. National Cancer Institute common toxicity criteria (NCI-CTC), versjon 2.0.
2. WHO performance status

NCI CTC Toxicity scale Version 2.0

COMMON TOXICITY CRITERIA (NCI CTC)

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
			ALLERGY/IMMUNOLOGY		
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
			AUDITORY/HEARING		
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
			BLOOD/BONE MARROW		
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges: children (≤ 18 years) younger adults (19-59) older adults (≥ 60 years)	 90% cellularity average 60-70% cellularity average 50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment

Toxicity	0	1	2	3	4
		Grade			
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other) Also consider Haptoglobin, Hgb.	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.		*≥75 - <100% LLN*	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.		*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT: Also consider Platelets.	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Transfusion: pRBCs	none	-	-	Yes	-
For BMT: Also consider Hemoglobin.	none	≤2 u pRBC (*≤15cc/kg*) in 24 hours elective or planned	3 u pRBC (*>15 ≤30cc/kg*) in 24 hours elective or planned	≥4 u pRBC (*>30cc/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Blood/Bone Marrow-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
		CARDIOVASCULAR (ARRHYTHMIA)			
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations Note: Grade palpitations only in the absence of a documented arrhythmia.	none	present	-	-	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac- ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T-wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/ml	≥ 0.05 - < 0.1 ng/ml	≥ 0.1 - < 0.2 ng/ml	≥ 0.2 ng/ml
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting). Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category. *For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.*					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	physiologic consequences resulting from symptoms	tamponade (drainage or pericardial window required)

Toxicity	Grade 0	1	2	3	4
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial) Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category. Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.	none	-	present	-	-
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation) Also grade Platelets. Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine. Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia) Note: See Appendix III for performance status scales.	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae) Also consider Hyperglycemia, Hypokalemia.	absent	-	present	-	-
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000ml of diarrhea/day	>1000 - ≤1500ml of diarrhea/day	>1500ml of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 ml/kg of diarrhea/day*	*>10 - ≤15 ml/kg of diarrhea/day*	*>15 ml/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing) Note: If toxicity is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Dysphagia- esophageal related to radiation Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- esophageal.	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly liquid, pureed or soft diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation. Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation. Note: Grade radiation mucositis of the larynx here. Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension. Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation. Note: Fistula is graded separately as Fistula- rectal/anal. Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-

Grade					
Toxicity	**0**	**1**	**2**	**3**	**4**
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, or radiographic documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding. If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs. Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as a toxicity.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN

Toxicity	Grade 0	1	2	3	4
Bilirubin- graft versus host disease (GVHD) Note: The following criteria are used only for bilirubin associated with graft versus host disease.					
	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Note: Documented viral hepatitis is graded in the INFECTION category.					
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This toxicity criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	>5.0 x ULN
Bicarbonate	WNL	< LLN - 16 mEq/dl	11 - 15 mEq/dl	8 - 10 mEq/dl	< 8 mEq/dl
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia is graded in the PAIN category.					
Myositis (inflammation/damage of muscle) Also consider CPK. Note: Myositis implies muscle damage (i.e., elevated CPK).	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis Also consider Headache, Vomiting, Fever.	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness Note: Syncope (fainting) is graded in the NEUROLOGY category.	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration- anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration- depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration- euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus Also consider Vision-double vision.	absent	present	-	-	-
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting) Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.	absent	-	-	present	-
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
			OCULAR/VISUAL		
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
			PAIN		
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Toxicity	Grade 0	1	2	3	4
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					

Toxicity	Grade 0	1	2	3	4
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine *Note: Adjust to age-appropriate levels for pediatric patients.*	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and uristix reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastastic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling

Toxicity	Grade 0	1	2	3	4
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare Also consider Hypercalcemia. Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Tumor lysis syndrome Also consider Hyperkalemia, Creatinine.	absent	-	-	present	-
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

WHO PERFORMANCE STATUS	
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to do light work
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled, cannot carry on any self care, totally confined to bed or chair.